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(54) Title: PREPARATION OF PREGELATINIZED HIGH AMYLOSE STARCH AND DEBRANCHED STARCH USEFUL AS AN EXCIPIENT FOR CONTROLLED RELEASE OF ACTIVE AGENTS

(57) Abstract

A process is disclosed for the manufacture of an excipient useful for the controlled release of an active agent. In this process, a starting material consisting of starch or high amylose starch is subjected to a gelatinization in an aqueous medium. When the starting material consists of starch having an amylose content of less than 50 % by weight, the gelatinized material is subjected to an enzymatic debranching treatment so as to obtain a gelatinized debranched starch having a short amylose chain content of at least 50 % by weight. When the starting material consists of starch having an amylose content of at least 50 % by weight or of a high amylose starch having an amylose content up to 80 % by weight, the gelatinized material is optionally subjected to an enzymatic debranching treatment so as to obtain a gelatinized debranched starch having a short amylose chain content of 20 % to 50 % by weight. The so obtained gelatinized and optionally debranched starch is further subjected to a thermal dehydration in order to obtain the requested excipient in form of a powder. Also disclosed is a dosage administration form for the sustained release of one or more active agents in the form of a powder. This form which is preferably a tablet, comprises the active agent(s) in admixture with the above excipient in such an amount as to achieve the requested sustained release.

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Preparation of pregelatinized high amylose starch and debranched starch useful as an excipient for controlled release of active agents

FIELD OF THE INVENTION

The present invention relates to a process for the manufacture of tablet excipients for use in the pharmaceutical industry.

More particularly, it relates to an economical process for the industrial manufacture in an aqueous medium of sustained release excipients comprising an enzymatically debranched starch or a pregelatinized high amylose starch.

The invention also relates to the debranched starch and the pregelatinized high amylose starch prepared by this process. These starches are suitable as excipients for the preparation of tablets, pellets, pills and granules.

The invention further relates to the use of these excipients for the preparation of tablets or other dosage administration forms for sustained release of active agents.

BACKGROUND OF THE INVENTION

One of the most pressing problems facing the pharmaceutical industry today is that in the past few years, only a very limited number of new drug products have been approved for marketing by the Food and drug administration (FDA). The lack of FDA-approved drugs, the high cost of new drug development, and the expiration of patents for existing drugs means that many pharmaceutical companies will be faced with a decreasing number of patent-protected drugs from which they may generate revenue. Development of novel methods of delivering these drugs may not only expend the patent life of the existing drugs but also minimize the scope and expenditure of testing required for FDA approval [Controlled-Release Drug Administration: Logic, by Y.W.Chien in Novel Drug Delivery Systems, vol. 14, chap. 1, Marcel Dekker, New York, 1982].

In this context, many efforts were devoted to the development of new excipients for the controlled release of drugs by various routes of administration. In the recent years, particular emphasis has been placed on the oral administration of drugs and, among the multitude of forms in which the drug may be so-dispensed, the

compressed tablet form is the one that has been the most frequently employed.

In addition to the active ingredient(s), tablets usually contains several inert substances, referred to as excipients, in sufficient amount to accomplish the desired effect. Excipients are generally classified by their functions and the major types used are fillers or diluents, binders, disintegrants, binder-disintegrants, lubricants and glidants [see for example "Compressed tablets" by B. B. Sheth et al in Pharmaceutical dosage forms, vol. 1, chap. 3, p 109-185, H. A. Lieberman and L. Lachman, Marcel Dekker, New York 1980]. Other specific excipients that are commonly used include colorants, sweeteners, flavors and the like.

Further specific excipients that are commonly used in this field consist of "slow release" excipients that are usually made of polymers selected to prolong and sustain the release of actives ingredients [see for example U.S. pat no. 3,087,860; U.S. pat. no. 2,987,445]. Use of polymers in the area of controlled delivery really began in the 1960's. Colin [Colin D. M., Hydrophilic matrix sustained release systems based on polysaccharide Carriers, Critical Reviews in Therapeutic Drug Carrier Systems, 8 (4), 1991, 395-421.] have reported that hydrophilic matrices prepared with polysaccharides and their derivatives are polymers of choice as the rate controlling carriers for these systems.

Among the polysaccharidic material, starch is one of the most interesting polymer used in the field. Starch is a natural carbohydrate and is considered to be the most important source of energy in plants. It is composed of two distinct fractions, namely (1) amylose which is a non-ramified fraction containing about 4,000 glucose units joint by α-1,4 links, and (2) amylopectin which is a branched fraction composed of about 100,000 glucose units. Starch is a natural occurring diluent but it can also be used as a tablet disintegrant agent. Starch can be modified through physical, chemical or enzymatic processes.

Pregelatinized common starch contains usually 20 to 30 % w/w of amylose. It is produced by gelatinization directly followed by a thermal dehydration process like drum-drying, spray drying or extrusion. It is commonly used in the place of starch, as a filler and binder-disintegrating agent. However, Nakano et al. [Nakano M., Nakazono N. and Inotsume N., Preparation and evaluation of sustained release tablets prepared with a-starch, Chem. Pharm. Bull. 35 (1987) 4346-4350] has already

reported that pregelatinized starch may also be used as sustained release hydrogels.

Herman et al. [Herman J. and Remon J. P., Modified starches as hydrophilic matrices for controlled oral delivery. II. In vitro drug release evaluation of thermally modified starches, International Journal of Pharmaceutics, 56 (1989) 65-70] have investigated the effect of many parameters on the sustained release properties of pregelatinized starch. They have concluded that the ratio amylose/amylopectin is the most important factor influencing swelling characteristics and *in vitro* drug release rate. Tablets made with common pregelatinized starch and tested *in vitro* (25 % of amylose w/w) are reported to splits into two parts resulting in a burst of drug release because of an increase in free surface area. In their article, Herman et al. have also concluded that pregelatinized high amylose starch (70% of amylose) do not form a coherent gel layer and do not sustain release. Pregelatinized waxy corn starch (100 % of amylopectin w/w and amylose free) is reported to form a gel layer during hydration and to decrease the drug release rate. However, the swollen gel layer of the amylose free starches (amylopectin) are reported to be very weak and the *in vivo* tablet erosion may considerably accelerate the drug release.

Visavarungroj et al. [Visavarungroj N., Herman J. and Remon J. P., Cross-linked starch as sustained release agent, Drug Development and Industrial Pharmacy, 16, (7), 1091-1108, 1990] have also disclosed that cross-linked waxy starches (amylose free starches) could be used as filler and disintegrant but are not recommended to use as a hydrophilic matrix in a sustained release formulation.

Milojevic et al. [Milojevic S.et al, Amylose, the new perspective in oral drug delivery to the human large intestine, STP Pharma Sciences 5(1) 47-53 (1995)] teach the preparation of coated pellets using a mixture of amylose and ethylcellulose as a coating excipient to suppress drug release over a period of 12h. The amylose-Ethocel® mixture may be used in the formulation of an a-amylase resistant coating for the drug delivery to the human large intestine. In this article, amylose is extracted from starch by sequential aqueous leaching in hot water and then is isolated as a complex with the addition of butanol-1. This article also reports that amylose alone is unsatisfactory as a coating material and that the butanol-treated amylose must actually be mixed with at least 60% of ethylcellulose to be efficient.

Modified and/or cross-linked starches are known to be powerful disintegrating agents with poor binding properties [see U.S. pat. No. 3,622, 677 and U.S. pat no. 4,369,308]. Usually, starch granules are cross-linking to increase their resistance to shear or to prevent gelatinization when heated, thereby permitting utilization of cross-linked starch granules in applications which would destroy granules of unmodified starch. The preparation of modified and/or cross-linked starch is well known in the art and such preparation is described in numerous text books or publications [see for example "Starch derivatives: production and uses" by M. W. Rutenberg and D. Solarek in Starch chemistry and technology, 2nd ed., chap. x, p. 311-379, R. L. Whistler, J. N. BeMiller and E. F. Paschall, Academic Press, 1984]. Only a few investigators have reported that cross-linked pregelatinized starch can be used as a sustained release agent. Kost et al. [Kost J. and Shefer S., Chemically-modified polysaccharides for enzymatically-controlled oral drug delivery, Biomaterials 11 (1990) 695-698] teach the preparation and use of starch ionically cross-linked starch by calcium chloride for entrapment and controlled release of bioactive molecules. The drug release rate is reported to be greatly affected by α-amylase activity. Van Aerde et al. [Van Aerde P. and Remon J. P., *in vitro* evaluation of modified starches as matrices for sustained release dosage form, International Journal of Pharmaceutics, 45, 145-152 (1988)] also reports that increasing the degree of cross-linking of pregelatinized starch increases the tablet drug release rate.

Mateescu et al. [see U. S. pat. No. 5,456,921 to Labopharm Inc.] teach how to prepare cross-linked amylose useful as a sustained release excipient. The so-prepared cross-linked amylose has a cross-linking degree from 0.1 to 10 % (based on the quantity of epichlorohydrin used to cross-link 100 g of high amylose starch). It is prepared by a water-miscible organic solvent process. In the description of the patent, it is demonstrated that pregelatinized high amylose starch (not cross-linked) is not suitable as a sustained release excipient. In fact, tablets made of 400 mg of pregelatinized high amylose starch containing 100 mg of theophylline released the totality of the drug in about 1.2 hours only.

Cartilier et al. [see International laid-open patent no. WO94/21236 to Labopharm Inc.] teach that cross-linked amylose having a cross-linking degree of 6

to 30, can be used as a binder and/or disintegrant agent for the preparation of tablets by direct compression. The binding properties of this product are reported to be definitively superior to starch. The quality of the binding and the controlled release properties of cross-linked amylose are closely related to the cross-linking degree and to the relative amount of amylose present in the starch used for the manufacture.

Mateescu et al. [see International laid-open patent no. WO94/02121 to Labopharm] also describe the association of α-amylase in tablets made of cross-linked amylose in view of increasing the dissolution rate of low soluble drugs.

Recently, Dumoulin et al.[see U. S. application serial No 08/800,518 to Rougier Inc.] have described an economical and industrial aqueous process for the manufacture of a tablet excipient, and in particular, to a slow release excipient mainly composed of cross-linked amylose useful in the preparation of controlled release dosage form by direct compression.

Wai-Chiu [see European patent EP-A-449,648 to National Starch] teach how to prepare a tablet binding-disintegrating excipient by enzymatic debranching of starch. The starch product obtained is characterize by a content of at least 20 % of short chain amylose by weight. Short chain amylose as such or modified and /or cross-linked short chain amylose resulting from the enzymatic debranching of starch prior to after chemical modification, can be used as a binder-disintegrant in tablets. It is reported that the binding-disintegrating properties of such products increase with the quantity of short amylose chains produced by the hydrolysis of amylopectin . It is reported by Wai-Chiu that pregelatinized high amylose starch containing at least 50 % of long chain amylose is also useful as a binder/disintegrant.

Arends-Scholte et al. [see International laid-open patent no. WO96/09815 to Cooperaieve Verkoop-Enproductiev-Ereniging Van Aardappelmeel En Derivaten Avebe B.A.] teach how to manufacture a tablet excipient from disintegrated starch granules prepared by enzymatic debranching of starch and characterized by a content of long chain amylose of at least 10 % by weight based on the amount of drug. In the description of this laid-open application, it is shown that a tablet manufactured with a starch product containing 65 % of long chain amylose and 35 % of short chain amylose which has not been dehydrated with ethanol, disintegrates and is therefore not suitable as a sustained release excipient.

Te Wierik et al [Te Wierik G.H.P., Eissens A.C., Besemer A.C. and Lerk C.F., Preparation, characterization and application of amylodextrin, metastable amylodextrins and metastable amylose, Pharmaceutical Research, vol. 10, No. 9, 1993] teach how to prepare amylodextrin by enzymatic hydrolysis of waxy maize starch with Pullulanase. The resulting soluble fraction of amylodextrin is freeze-dried or dehydrated by treatment with organic solvent as ethanol. They also report the successful application of amylodextrin as an excipient in the preparation of controlled release systems. They further report that all amylodextrin tablets tested *in vitro* showed fracturing on immersion in the dissolution medium. Te Wierik et al [Te Wierik G.H.P., Van der Veen J., Eissens A.C. and Lerk C.F., Preparation, characterization and application of linear dextrins. Part VI. General applicability and mechanism of programmed release from amylodextrin tablets, J. Control. Release, 27 (1993) 9-17]. Dissolution profile and release kinetics may be altered by the presence of tablet fracturing and this may lead to a lack of reproducibility of the system.

Te Wierik et al [Te Wierik G.H.P., Eissens A.C.,Bergsma J., Arends-Scholte A.W., Lerk C.F., A new generation of starch products as excipient in pharmaceutical tablets. II. High surface area retrograded pregelatinized potato starch products in sustained-release tablets, J. Control. Release, 45 (1997) 25-33] also teach the preparation of new linear short chain starch of high specific surface area possessing sustained release properties. The short chain starch is prepared by gelatinization of potato starch followed by a complete degradation of amylopectin using a debranching enzyme (Pullulanase) and a controlled enzymatic hydrolysis of amylose chain using α-amylase. The short chain starch of high specific surface area is obtained following a precipitation (retrogradation), filtration and dehydration by freeze-drying or by substitution of water by alcohol or acetone prior to air drying. It is reported that low surface area linear product obtained by thermal dehydration (drying at room or elevated reference temperatures or spray drying) do not have sustained release properties and quickly disintegrate.

Te Wierik et al. [Te Wierik G. H. P., Eissens A. C., Besemer A. C. and Lerk C. F., Preparation, characterization, and pharmaceutical application of linear dextrins. I. Preparation and characterisation of amylodextrin, metastable amylodextrins, and metastable amylose, Pharmaceutical Research, vol 10, no 9,

1993] further teach the preparation of metastable amylose useful as sustained release excipient. Metastable amylose is prepared by complexation of amylose V® supplied by AVEBE, with 2-methyl-1-butanol followed by a dehydration with ethanol [Te Wierik G.H.P., Eissens A.C., Bergsma J., Arends-Scholte A.W., Lerk C.F., A new generation of starch products as excipient in pharmaceutical tablets,..., J. Control. Release, 45 (1997) 25-33]. Te Wierik et al also report and insist on the fact that pregelatinized high amylose starch do not sustained release and long chain linear amylose (amylose V®) must be dehydrated using an organic solvent (ethanol) to obtain sustained release properties. However, water front penetration into tablets made of metastable amylose has a higher deviation from linear kinetics than into amylodextrin tablets.

As may be appreciated, none of the starch products briefly disclosed hereinabove display all of the desirable sustained release properties. In fact, due to the high production cost and the complexity of the manufacturing processes, there is a need for a low cost starch which is suitable as sustained release excipient.

Until now, the literature has demonstrated that pregelatinized high amylose starch (70 % of amylose w/w) seems not to be suitable as a hydrophilic matrix in a sustained release formulation and that debranched starch must be dehydrated using an organic solvent to obtain sustained release properties.

SUMMARY OF THE INVENTION

An object of the present invention is to provide an economical process for the industrial manufacture in an aqueous medium of pregelatinized high amylose starch possessing unpredictable sustained release properties.

Another object of the invention is to provide a process for the industrial manufacture by aqueous processing and thermal dehydration, of an enzymatically debranched starch having the same desired sustained release properties as presently obtained by ethanol treatment.

A further object of the invention is to provide an excipient useful for the controlled release of an active agent, the excipient being in the form of a powder and being obtained by any one of the above process.

Still another object of the invention is to provide tablets or similar oral

dosage forms containing the so-prepared pregelatinized high amylose starch or debranched starch as a suitable excipient for controlled release of the active agent(s) contained in the tablets.

The process according to the invention as broadly claimed hereinafter comprises the steps of:

a) providing a starting material selected from the group consisting of starch and high amylose starch;

b) subjecting the starting material to a gelatinization in an aqueous medium;

c) when the starting material consists of starch having an amylose content of less than 50% by weight, subjecting said gelatinized material to an enzymatic debranching treatment so as to obtain a gelatinized debranched starch having a short amylose chain content of at least 50% by weight; and

when the starting material consists of starch having an amylose content of at least 50% by weight or of a high amylose starch having an amylose content up to 80% by weight, optionally subjecting said gelatinized material to an enzymatic debranching treatment so as to obtain a gelatinized debranched starch having a short amylose chain content of 20% to 50% by weight, and

d) subjecting the gelatinized and optionally debranched starch to a thermal dehydration in order to obtain the requested excipient in form of a powder.

The excipient that is so obtained is useful for the controlled release of an active agent. This excipient which is also claimed hereinafter in the form of a powder and can be used for the manufacture of a dosage administration form for the sustained release of at least one active agent in the form of a powder. This form comprises said at least one active agent in admixture with an excipient according to the invention. This excipient being present in such an amount as to achieve the requested sustained release.

The basic steps of the process according to the invention as broadly defined hereinabove are as follows.

Gelatinization

The process according to the invention for the industrial manufacture of

starch products useful as excipient for controlled release of active agents comprises a first step of gelatinization, that is common to all kinds of starting materials.

It is known that Micellar crystallites held together by hydrogen bonding between amylopectin and amylose are responsible for the integrity of starch granules. When aqueous suspension of starch is heated to a certain temperature (gelatinization), the hydrogen bonding weakens and the granules swell until collapsing.

There are numerous methods of gelatinization of starch that are known in the art, including direct or indirect heating of an aqueous dispersion of starch, chemical treatment using a strong alkali or the combination of a mechanical and heat treatment.

Pregelatinized starch is known to be soluble in cold water. At first sight, one could argue that gelatinization of starch should not be desirable to obtain a controlled release excipient. However, it has been found that the gelatinization of starch is essential to achieve leaching of amylose from granules of starch in view of obtaining release properties.

Optional debranching

As reported in the prior art, most starch granules contain two types of polymers: amylose (5-75% by weight based on dry substance) and amylopectin (25-95% by weight based on dry substance). Amylose is essentially a long linear molecule whereas amylopectin is a highly branched molecule. Amylopectin may be debranched by treatment with a debranching enzyme, such as Pullulanase and isoamylase. After such treatment the resulting starch will essentially be composed of long amylose chains and short amylose chains in a ratio depending of the initial amylopectin content and the efficiency of the enzymatic treatment.

In accordance with the invention, the starch product that is being used for the preparation of the excipient, must contain at least 50% by weight of amylose. Therefore, if use is made of high amylose starch (*viz.* a starch already containing 50% by weight or more of amylose), debranching is optional. However, if use is made of "common" starch (*viz.* a starch containing from 20 to 50% by weight of amylose only) or of "waxy" starch, it is necessary to subject the gelatinized starch to

a debranching step, in which the amylopectin molecules are hydrolysed with a suitable enzyme, *viz.* Pullulanase.

Drying

The process according to the invention further comprises a drying step which must be carried out in order to dry the gelatinized high amylose starch or debranched starch that have been prepared.

Numerous methods are described in the literature for drying gelatinized starch: such as drum-drying or spray drying techniques using spray nozzle or atomisation disc. However, according to the literature, the pregelatinized high amylose starch prepared by the drying method mentioned above is supposedly not to be suitable as a sustained release excipient.

In accordance with the present invention, it has surprisingly been found that gelatinized high amylose or debranched starch prepared in an aqueous medium and thermally dehydrated, are particularly useful and efficient as a sustained release excipient.

Among the numerous aqueous thermal method that can be used, spray drying is the one that is particularly preferred in accordance with the invention.

Optional thermal treatment

As is already disclosed in U.S. application No. 08/800,518 to Dumoulin et al, if the pregelatinized starch or the debranched starch is cooled and kept at a temperature in the range of 1 to 20°C for transportation or any other reason, the starch product must be thermally treated at a temperature higher than 100°C to obtain the sustained release properties.

Optional wet granulation

The particle size of the particles of starches powder obtained by spray drying is smaller than 50µm. Accordingly, it may be useful to subject the so-obtained powder to a granulation in order to enlarge the particle size and obtain uniform particles that will easily flow through a tablet machine hopper and feed frame into tablet dyes. Powder recovered from the spray dryer may be wet formulated in line

using a fluid bed granulator. Alternatively, such a powder can be granulated in a fluid bed or a V-blender.

Formulation

As aforesaid, the dried products that is so obtained can be used as an excipient for the manufacture of controlled release tablets or similar oral dosage forms.

In accordance with a preferred embodiment of the invention, the amylose starch or debranched starch that is so-obtained, can be admixed with small amounts of polymers such as *Carbopol®*, *Methocel®* or any similar adjuvant which becomes viscous in the presence of water and may fill the small cracks that are formed in the tablets during dissolution. Such permits to obtain a quasi zero order drug release without profile fluctuation. This addition is particularly useful and efficient for tablets. However, it is not compulsory for other dosage forms, such as granules.

The amount of drug contained in the dosage form may vary within a wide range, depending on the solubility of the drug. It is however preferred that the amount of drug in the form be lower than 60% by weight of the total weight of the form.

It is worth mentioning that, in addition to raw starches, chemically cross-linked or substituted pregelatinized starches are also eligible for use as starting materials in the process according to the invention. The cross-linking or substitution of the starch may be realized before or after hydrolysis of amylopectin molecules. If a moderate chemical modification of the starch is carried out prior to the hydrolysis, the debranching enzyme will still recognize and hydrolyse the amylopectin and convert it into short chain amylose.

The invention and its advantages will be better understood upon reading the following non-restrictive detailed description.

DETAILED DESCRIPTION OF THE INVENTION

1. Preparation of gelatinized high amylose starch

Step (1.a) Starch gelatinization by thermomechanical treatment

High amylose starch in the form of an aqueous dispersion (1 to 20% w/w based on dry weight) is preferably gelatinized in a scraped-surface heat exchanger at a temperature range of 110 to 160° C for 5 to 60 minutes depending on the amylose content, temperature and quantity introduced.

Step (1.b) Spray drying of the gelatinized high amylose starch

The so obtained aqueous gelatinized high amylose starch, at a concentration in the range of 0,5 to 15% w/w, most preferably in the range of 4 to 12% w/w, and at a temperature in the range from 20 to 90°C, most preferably from 40 to 70°C, can be spray dried using a spray nozzle or a rotating disc having an inlet temperature in the range of 175 to 350°C and an outlet temperature in the range of 60 to 135°C.

2. Preparation of gelatinized debranched starch

Step (2.a) Starch gelatinization prior to the enzymatic treatment

Like in the case of the high amylose starch, common starch or waxy starch can be gelatinized thermomechanically as described in step 1.a. However, it must thereafter be treated with a debranching enzyme.

Step (2.b) Hydrolysis of amylopectin molecules using Pullulanase

The aqueous solution of gelatinized starch (5 to 20% by weight based on dry substance) can be treated with Promozyne 200 L (Pullulanase) in the range of 0.1 to 10% (v/g based on weight of the dry substance) at a pH in the range of 3.5 to 6 and at temperature in the range of 35 to 65°C for 1 to 24 hours depending of the amylopectin content and the hydrolysis parameters chosen. The pH of the resulting debranched starch may be adjusted in a preferable manner between 6 and 7. The

debranching reaction is ended by heating the starch slurry at a temperature higher than 70°C until enzyme inactivation.

Step (2.c) Thermal dehydration of debranched starch

According to the literature, debranched starch must be dehydrated by water substitution with ethanol or acetone in order to obtain sustained release properties.

As aforesaid, in accordance with this invention, it has been found that debranched starch prepared in an aqueous medium and dehydrated by a thermal method is also offered as sustained release excipient.

Among the numerous aqueous thermal method described in the literature, debranched starch is preferably dehydrated (dried) by spraying drying an aqueous solution of debranched starch at a concentration in the range of 0,5 to 15% w/w, most preferably in the range of 4 to 12% w/w, at a temperature in the range from 20 to 90°C, most preferably from 40 to 70°C. Such a spray drying can be carried out with a spray nozzle or rotating disc having an inlet temperature in the range of 175 to 350°C and an outlet temperature in the range of 60 to 135°C.

3. Test methods

Despite the fact that drug dosage oral forms may be prepared in a multitude of form, tablets obtained by direct compression have been chosen to evaluate and illustrate the sustained release properties of starch products according to the invention.

The sustained release property of the tablets made of starch products were evaluated using the following *in* vitro dissolution test.

Preparation of the tablets:

Tablets of 400 mg (diameter of 12 mm and thickness of 2.9 mm) containing 20% of acetaminophen as model drug, from 5 to 20% of *Carbopol 940*® or from 10 to 20% of hydroxypropyl-methyl cellulose (HPMC) K100M (*Methocel*® and from 60 to 75% w/w of starch products according of the present invention were prepared by direct compression of a mixture of powders of the drug and excipients in a die having flat-face punches, using a hydraulic press at 2.4 T/cm^2.

In vitro tablet dissolution

Method No. 1: Dissolution in phosphate buffer

Tablets were placed individually in 1 L of phosphate buffer in accordance with USP 23 p. 1791 (text <711>, 37°C at pH = 7) in a Distek dissolution apparatus equipped with paddles rotating at 50 rpm. The drug release was monitored spectrophotometrically at 244 nm, recorded and analysed with a Hewlett Packard dissolution system.

Method No. 2: Dissolution in a solution containing 18000 EU of α-amylase

Tablets were placed individually in 1 L of phosphate buffer containing 18000 EU of α-amylase (one enzyme unit releases 1 mg of maltose into 3 minutes at 20°C and pH 6,9) in accordance with USP 23 p. 1791 (test <711>, 37°C at pH = 7) in a Distek dissolution apparatus equipped with paddles rotating, at 50 rpm. The drug release was monitored spectrophotometrically at 244 nm, recorded and analysed with a Hewlett Packard dissolution system.

Example 1: Preparation of gelatinized high amylose starch containing 70% w/w of amylose, using a thermomechanical gelatinization pretreatment followed by a spray drying

Gelatinization

High amylose starch containing 70 % w/w of amylose was first gelatinized. To do so, 266 kg of an aqueous dispersion of 14 % solids w/w (based on the dry starch) was introduced at a rate of 1 Kg/min in a scraped-surface heat exchanger a temperature in the range of 150 to 160°C. The gelatinized product was recovered and maintained under agitation at 65°C until the next step.

Spray drying of the gelatinized high amylose starch

The gelatinized product recovered from the previous step was diluted to 7% of solids w/w (based on the dry starch) with hot soften potable water. The product was maintained at 50°C under agitation and sprayed in a Niro spray dryer model P6.3

having a water evaporating capacity of 50 Kg/h, equipped with a atomizer disc, with an inlet temperature of 300 °C and an outlet temperature of 120°C.

EXAMPLE 2: Formulation of tablets with pregelatinized high amylose starch (70% w/w of amylose) and *Carbopol*® and with pregelatinized high amylose starch (70% w/w of amylose) and *Methocel*®

(a) Tablets of 400 mg (diameter of 12 mm and thickness of 2.9 mm) containing 20% w/w of acetaminophen as a model drug, 60 or 70 or 75% w/w of pregeletanized high amylose starch and respectively 20 or 10 or 5% w/w of *Carbopol*® 940 were prepared by direct compression of a mixture of powders of these ingredients in a hydraulic press at 2.4 T/cm^2. The *in vitro* dissolution method No. 1 described hereinabove was used to evaluate the sustained release properties of the so-prepared tablets. The results are presented in Table 1.

(b) Tablets of 400 mg diameter of 12 mm and thickness of 2.9 mm containing 20 % w/w of acetaminophen as model drug, 60 or 70 % of pregelatinized high amylose starch and respectively 20 or 10 w/w *Methocel*® (HPMC K100M) were also prepared by direct compression of a mixture of powders of the ingredient in a hydraulic press at 2.4 T/cm2. The *in vitro* dissolution method No.1 described hereinabove was used to evaluate the sustained release properties of the so-prepared tablets. The results are presented in Table I.

TABLE I

	Type of starch	Excipients added	Time required to release the following % of the initial drug content of the tablet (expressed in hours)		
			30%	50%	90%
Example 2a	Pregelatinized 70% amylose starch	5% Carbopol	2.5	8	18
Example 2a	Pregelatinized 70% amylose starch	10% Carbopol	2.5	7	17
Example 2a	Pregelatinized 70% amylose starch	20% Carbopol	2.5	7	16
Example 2b	Pregelatinized 70% amylose starch	10% HPMC	3	10	24
Example 2b	Pregelatinized 70% amylose starch	20% HPMC	3	10.5	26

The dissolution test results presented in table I show the unsuspected and the impressive sustained release properties of pregelatinized high amylose containing starch (containing 70 % of amylose).

The tablets containing 5 and 10 % of *Carbopol*® 940 that were recovered after the dissolution test (25 hours), were practically unswollen. They were showing small cracks but had excellent mechanical properties (resistant and elastic). These cracks seemed to be filled by the viscous polymer added in the tablets formulation,

thereby permitting to obtain a quasi zero order drug release without profile fluctuation. As a matter of fact, the addition of 5 % of Carbopol 940 in the preparation of acetaminophen tablets was sufficient to fill the small cracks formed in the tablets. However, the addition of more than 5 % of *Carbopol*® slightly increase the drug release rate. In fact, tablets containing 20 % of *Carbopol*® were almost completely eroded at the end of the dissolution (after 16 hours or immersion).

Drug release from tablets made of pregelatinized high amylose starch and HPMC K100M was even more striking. In fact, the time required to release 90 % of the initial acetaminophen tablet content was about 25 hours. As reported for tablets containing *Carbopol*®, tablets recovered after completion of the dissolution test (almost 40 hours) were practically unswollen. They were showing small cracks but had excellent mechanical properties (resistant and elastic). The addition of at least 10 % of HPMC was sufficient to fill the small cracks of the tablets, thereby permitting to obtain a quasi zero order drug release without profile fluctuation. The addition of more than 10 % of HPMC seemed not to have an important effect on the drug release and mechanical properties of tablets.

This example fully illustrates the sustained release properties of pregelatinized high amylose starch containing 70 % of amylose, as produced by the aqueous process according to the present invention.

Tablets prepared without viscous agent and tested *in vitro* still had drug sustained release properties but showed fracturing after a few hours (4 to 8 hours) of immersion in the dissolution medium. Thereby, some fluctuation in the drug release profile was observed. As demonstrated hereinbefore, the addition of a low quantity of viscous agent improves the linearity of the drug release profile. One skilled of the art will know that the beneficial effect of *Carbopol*® 940 or HPMC K100M on the drug release linearity may also be obtained with many other viscous polymers. He or she will also knows that the amount of viscous agent needed to obtain the beneficial effect will depend on the dosage form (tablet, pellet, beds), on the nature and quantity of drug and, of course, on the viscous agent used.

EXAMPLE 3: Preparation of gelatinized high amylose starch (containing 50 % w/w of amylose) using a thermomechanical gelatinization pretreatment followed by spray drying

Gelatinization

High amylose starch containing 50 % w/w of amylose was first gelatinized. To do so, 323 kg of an aqueous dispersion of 7 % solids w/w (based on the dry starch) was introduced at a rate of 1 Kg/min in a scraped-surface heat exchanger a temperature in the range of 150 to 160°C. The gelatinized product was recovered and maintained under agitation at 65°C until the next step.

Spray drying of the gelatinized high amylose starch

The gelatinized product recovered from the previous step (7% of solids w/w based on the dry starch) was maintained at 55°C under agitation and spray-dried in a Niro spray dryer model P6.3 having an inlet temperature of 300°C and an outlet temperature of 100°C.

EXAMPLE 4: Formulation of tablets with pregelatinized high amylose starch (50 % w/w of amylose) and *Carbopol*® and with pregelatinized high amylose starch (50% w/w of amylose) and *Methocel*®

(a) Tablets of 400 mg (diameter 12 mm and thickness of 2.9 mm) containing 80 mg of acetaminophen as model drug, 300 mg of pregelatinized high amylose starch (containing 50 % w/w of amylose) and 20 mg of *Carbopol*® 940 were prepared by direct compression of a mixture of powders of these ingredients in a hydraulic press at 2.4 T/cm^2. The *in vitro* dissolution method No. 1 described hereinabove was used to evaluate the sustained release properties of the so-prepared tablets. The results are presented in Table II.

(b) Tablets of 400 mg (12 mm diameter and thickness of 2.9 mm) containing 80 mg of acetaminophen as model drug, 280 mg of pregelatinized high amylose starch (containing 50% w/w of amylose) and 40 mg of *Methocel*® (HPMC K100M)

were prepared by direct compression of a mixture of powders of these ingredients in a hydraulic press at 2.4 T/cm^2. The *in vitro* dissolution method No. 1 herein described was used to evaluate the sustained release properties of the so-prepared tablet. The results are presented in Table II.

TABLE II

	Type of starch	Excipients added	Time required to release the following % of the initial drug content of the tablet (expressed in hours)		
			30%	60%	90%
Example 4a	Pregelatinized 50% amylose starch	5% Carbopol	2	6	14
Example 4b	Pregelatinized 50% amylose starch	10% HPMC	2	7	17

The dissolution test results presented in Table II sho that pregelatinized high amylose starch containing 50% amylose possess also unsuspected sustained release properties. However, the drug release from tablets made of these starch was faster than the one obtained with pregelatinized starch containing 70% of amylose, thereby suggesting that the higher is the amylose content, the better will be the sustained release properties.

The tablets containing 5% of *Carbopol*® and 10% of HPMC that were recovered after the dissolution test, were practically unswollen. They were showing much more small cracks but still had good mechanical properties (resistant and elastic). Thus, the addition of *Carbopol*® or HPMC permits to fill the tablets cracks and to obtain a quasi zero order drug release without profile fluctuation.

Drug release from tablets made of pregelatinized starch containing 50 % of amylose and 10 % of HPMC K100M was longer than the one obtained from tablets

containing *Carbopol*®. In fact, the time required to release 90 % of the initial acetaminophen tablet content was about 17 hours.

EXAMPLE 5: Preparation of gelatinized starch containing about 20 % of amylose using a thermomechanical gelatinization pretreatment followed by a spray drying

The purpose of this example is to compare the sustained release properties of starch produced by the process according to this invention and to demonstrate the beneficial effect of amylose on such properties.

Gelatinization

Common starch containing about 20 % w/w of amylose was first gelatinized. To do so, 109 kg of an aqueous dispersion of 8 % solids w/w (based on the dry starch) was introduced at a rate of 1 Kg/min in a scraped-surface heat exchanger a temperature in the range of 135 to 145°C. The gelatinized common starch was recovered and maintained under agitation at a 60°C until the next step.

Spray drying of the gelatinized common starch

The gelatinized common starch recovered from the previous step (8 % w/w based on the dry starch) was maintained at a temperature in the range of 50 to 60°C under agitation and spray dried in a Niro spray dyer model P6.3 having an inlet temperature of 280°C and an outlet temperature of 126°C.

EXAMPLE 6: Formulation of tablets with pregelatinized common starch and *Carbopol*® and with pregelatinized common starch and *Methocel*®

(a) Tablets of 400 mg (diameter of 12 mm and thickness of 2.9 mm) containing 20 % of acetaminophen as a model drug, 75 % of pregelatinized common starch and 5 % of *Carbopol*® 940 were prepared by direct compression of a mixture of powders of these ingredients in a hydraulic press at 2.4 T/cm2. The *in vitro*

dissolution method No.1 described hereinabove was used to evaluate the sustained release properties of the so prepared tablets containing the pregelatinized common starch prepared in example 5. The results are presented in Table III

(b) Tablets of 400 mg (diameter of 12 mm and thickness of 2.9 mm) containing 20% w/w of acetaminophen as a model drug, 70% w/w of common starch and 10% w/w of *Methocel*® of HPMC K100M) were prepared by direct compression of a mixture of powders of these ingredients in a hydraulic press at 2.4 T/cm2. The *in vitro* dissolution method No.1 described hereinabove was used to evaluate the sustained release properties of the so-prepared tablets. The results are presented in Table III.

TABLE III

	Type of starch	Excipients added	Time required to release the following % of the initial drug content of the tablet (expressed in hours)		
			30%	60%	90%
Example 6a	Pregelatinized 20% amylose starch	5% Carbopol	2	6	11
Example 6b	Pregelatinized 20% amylose starch	10% HPMC	2	7	15

As it is reported in the prior art, tablets made of gelatinized starch containing about 20 % of amylose and about 80 % of amylopectin are able to provide sustained release. However, as it was the case with pregelatinized high amylose starch containing 50 and 70 % of amylose, tablets recovered after the dissolution test, had some cracks. The drug release from tablets made according both formulations using *Carbopol*® or HPMC was faster than the one from tablets made of pregelatinized starch containing 50 and 70 % of amylose. In fact, the time required to release 90 % of the initial acetaminophen from tablets made of pregelatinized common starch

containing 10 % of HPMC was about 15 hours as compared to 24 hours with tablets made of pregelatinized starch containing 70 % of amylose. This result confirms that the role and quantity of amylose are decisive for achieving proper sustained release properties.

EXAMPLE 7: Preparation of debranched starch followed by spray drying

High amylose starch was used as starting material in this example. However, use could also be made of waxy maize starch containing 95 % w/w of amylopectin or of common starch containing from 20 to 50 % of amylose as starting materials.

Gelatinization

High amylose starch containing 70 % w/w of amylose was first gelatinized. To do so, 300 kg of an aqueous dispersion of 15 % solids w/w (based on the dry starch) was introduced at a rate of 1 Kg/min in a scraped-surface heat exchanger at a temperature in the range of 150 to 160°C. The gelatinized product was recovered and maintained under agitation at 70°C until the next step.

Hydrolysis of amylopectin molecules using Pullulanase

100 kg of gelatinized high amylose starch recovered from the previous step was transfer to a 200 L GOAVEC reactor tank. The temperature of the medium was cooled to 60°C and the pH was adjusted at 5. Promozyme 200 L (Novo-Nordisk) was added in order to obtain a Pullulanase enzyme concentration of 3 % v/w based on the dry weight of the gelatinized high amylose starch. The temperature was adjusted to 55°C and the hydrolysis was carried out for about 20 hours. Then, the reaction medium was diluted with 100 kg of soften potable water at 60°C and the pH was adjusted at 6.3. The debranching reaction was ended by heating the resulting debranched starch at 90°C for 20 minutes.

Thermal treatment of the debranched starch

The slurry of debranched starch recovered from the previous step was thermally treated in a scraped-surface heat exchanger at a temperature in the range of

150 to 160°C. The aqueous heat-treated debranched starch was maintained under agitation at 65°C until its subsequent dehydration by spray drying.

Spray drying of the aqueous suspension of debranched starch

The debranched starch recovered from the previous step (containing 7.5 % of solids w/w based on the dry starch) was kept at 65°C under agitation and spray dried in a Niro spray dryer model P6.3 having an inlet temperature of 300°C and an outlet temperature of 100°C.

EXAMPLE 8: Tablets formulation with debranched starch and *Methocel®*

(a) Tablets of 400 mg (diameter of 12 mm and thickness of 2.9 mm) containing 20% w/w of acetaminophen as a model drug, 75% w/w of debranched starch and 5% of *Carbopol®* 940 were prepared by direct compression of a mixture the powders of these ingredients in a hydraulic press at 2.4 T/cm2. The *in vitro* dissolution method No.1 described hereinabove was used to evaluate the sustained release properties of the tablets prepared with the debranched starch of example 7. The results are presented in Table IV.

(b) Tablets of 400 mg (diameter of 12 mm and thickness of 2.9 mm) containing 20% w/w of acetaminophen as a model drug, 70% w/w of debranched starch and 10% w/w of *Methocel®* HPMC K100M) were prepared by direct compression of a mixture of powders of these ingredients in a hydraulic press at 2.4 T/cm2. The *in vitro* dissolution method No.1 described hereinabove was used to evaluate the sustained release properties of the so-prepared tablets. The results are presented in Table IV.

TABLE IV

	Type of starch	Excipients added	Time required to release the following % of the initial drug content of the tablet (expressed in hours)		
			30%	60%	90%
Example 8a	Pregelatinized debranched starch	5% Carbopol	3	9	22
Example 8b	Pregelatinized debranched starch	10% HPMC	4	11	28

The dissolution test results presented in table IV show the unsuspected and striking sustained release properties of debranched starch subjected to thermal dehydration (spray drying). The tablets made of debranched starch containing 5 % of *Carbopol*® or 10 % of HPMC recovered after the dissolution test were practically unswollen. They were showing small cracks but still had good mechanical properties (resistant and elastic).

The addition of *Carbopol*® or HPMC permits to fill the tablets cracks and to obtain a quasi zero order drug release without profiles fluctuation. The drug release from tablets made of debranched starch containing HPMC K100M was longer than the one from tablets made with *Carbopol*®. In fact, the time required to release 90 % of the drug from tablets containing HPMC is very impressive, as it was about 28 hours.

EXAMPLE 9: Comparison of sustained release properties of starches prepared according to this invention in a dissolution medium containing 18000 UE of alpha-amylase

A comparison was made of the drug dissolution profiles of 400 mg tablets containing 80 mg of acetaminophen (20% w/w), 20 mg of *Carbopol*® (5% w/w) and

300 mg (75% w/w) of pregelatinized high amylose starch (prepared as disclosed in example 1 and containing 70 % of amylose); or

300 mg (75% w/w) of pregelatinized high amylose starch (prepared as disclosed in example 3 and containing 50 % of amylose); or

300 mg (75% w/w) of pregelatinized common starch (prepared as disclosed in example 7 and containing about 20 % of amylose);

or 300 mg (75% w/w) of debranched starch (prepared as disclosed in example 5 and containing about 70 % of long chain amylose and 30 % of short chain amylose).

The tablets were prepared by direct compression of a mixture of powders of these ingredients in a hydraulic press at 2.4 T/cm2. The *in vitro* dissolution method No. 2 described hereinabove was used to evaluate the sustained release properties of the so-prepared tablets. The resistance of the starch product to alpha-amylase is presented in Table V.

TABLE V

	Type of starch	Excipients added	Time required to release the following % of the initial drug content of the tablet (expressed in hours)		
			30%	60%	90%
Prepared as in Example 5	Pregelatinized 20% amylose starch	5% Carbopol	2	4.5	7
Prepared as in Example 3	Pregelatinized 50% amylose starch	5% Carbopol	2	5	11
Prepared as in Example 1	Pregelatinized 70% amylose starch	5% Carbopol	2	7	17
Prepared as in Example 7	Pregelatinized debranched starch	5% Carbopol	3	9	22

This example illustrates the high enzymatic resistance of starches rich in amylose content prepared by the aqueous process according to the invention. Tablets resistance to α-amylase increased when the ratio amylose/amylopectin increased. Tablets made of pregenatinized 20% amylose starch (common starch) were badly affected by the enzyme and, as a result, the time requested to release 90% of the drug dropped from 11 to 7 hours. Tablets made of pregelatinized 50% amylose starch were slightly affected by the enzyme and the time requested to release 90% of the drug dropped from 14 to 11 hours. Tablets made of pregelatinized 70% amylose starch were practically not affected by the enzyme (from 18 to 17 hours) and tablets made of debranched starch were the most resistant and were not affected by α-amylase. This high tablet resistance to enzyme is believed to be related to the property of the amylose chain to retrograde on hydration. The retrograded gel phase limits the subsequent tablet swelling, the drug diffusion and the enzymatic amylolysis. As it is reported in the art, retrograded pregelatinized starch are not attacked by α-amylase in the gastrointestinal tract. Thereby, the *in vivo* drug release will be independent of the fluctuation of the α-amylase in the human intestine.

Of course, numerous modifications could be made to the present invention as disclosed and exemplified hereinabove, without departing from the scope of the appended claims.

CLAIMS

1. A process for the manufacture of an excipient useful for the controlled release of an active agent, comprising the steps of:

a) providing a starting material selected from the group consisting of starch and high amylose starch;

b) subjecting the starting material to a gelatinization in an aqueous medium;

c) when the starting material consists of starch having an amylose content of less than 50% by weight, subjecting said gelatinized material to an enzymatic debranching treatment so as to obtain a gelatinized debranched starch having a short amylose chain content of at least 50% by weight; and

when the starting material consists of starch having an amylose content of at least 50% by weight or of a high amylose starch having an amylose content up to 80% by weight, optionally subjecting said gelatinized material to an enzymatic debranching treatment so as to obtain a gelatinized debranched starch having a short amylose chain content of 20% to 50% by weight, and

d) subjecting the gelatinized and optionally debranched starch to a thermal dehydration in order to obtain the requested excipient in form of a powder.

2. The process of claim 1, wherein:

in step b), the gelatinization consists of a thermo-mechanical treatment of an aqueous dispersion of the starting material.

3. The process of claim 2, wherein the aqueous dispersion contains from 1 to 20% by weight of the starting material and the thermo-mechanical treatment of this aqueous dispersion is carried out in a scraped-surface heat exchanger at a temperature ranging from 110 to 160°C for 5 to 60 minutes.

4. The process of any one of claims 1 to 3, wherein:

in step a), use is made of starch as starting material; and

in step c), the enzymatic debranching treatment is carried out with pullulanase at a pH in the range of 3.5 to 6 and a temperature in the range of 35 to 65°C for 1 to 24 hours.

5. The process of any one of claims 1 to 4, wherein:

in step d), the thermal dehydration is achieved by spray-drying of the gelatinized and eventually debranched material in the form of a solution that contains from 0.5 to 15% by weight of said material and is at a temperature of 20 to 90°C.

6. The process of claim 5, wherein the spray-drying is carried out with a spray-nozzle or rotating disc having an inlet temperature of 175 to 350°C and an outlet temperature of 60 to 135°C.

7. The process of claim 6, wherein the solution contains from 4 to 12% by weight of the gelatinized and eventually debranched material and is at a temperature of 40 to 70°C.

8. The process of any one of claims 1 to 7, comprising the additional step of :

c') prior to carrying out step d), subjecting the gelatinized and eventually debranched material to a thermal treatment at a temperature higher than 100°C.

9. The process of any one of claims 1 to 8, comprising the additional steps of:

e) subjecting the powder obtained in step d) to a granulation.

10. The process of claim 9, wherein, in step e), the granulation is a wet granulation carried out in a fluid bed or high shear granulator.

11. The process of claim 9, wherein, in step e), the granulation is a dry granulation carried out in a roller compaction apparatus.

12. The process of any one of claims 1 to 11, wherein:
in step a), the starting material that is provided is a high amylose starch containing at least 50% by weight of amylose.

13. The process of claim 12, wherein the high amylose starch used as starting material contains 70% by weight of amylose.

14. The process of any one of claims 1 to 11, wherein:
in step a), the starting material that is provided is a common or waxy starch.

15. The process of claim 14, wherein said common or waxy starch is cross-linked or substitute.

16. An excipient useful for the controlled release of an active agent, said excipient being in the form of a powder and being obtained by the process of any one of claims 1 to 15.

17. A dosage administration form for the sustained release of at least one active agent in the form of a powder, said form comprising said at least one active agent in admixture with an excipient as claimed in claim 16, said excipient being present in such an amount as to achieve the requested sustained release.

18. The dosage form of claim 17, containing at least 20% by weight of said excipient.

19. The dosage form of claim 17, containing at least 60% by weight of said excipient.

20. The dosage form of claim 17, containing at least 94% by weight of said excipient.

21. The dosage form of claim 18 or 19, further containing up to 40% by weight a polymer that becomes viscous in the presence of water and thus may fill cracks formed in the form during its dissolution.

22. The dosage form of claim 21, wherein said polymer is selected from the group consisting of *Carbopol*® and *Methocel*®.

23. The dosage form of claim 22, wherein said polymer is *Carbopol*® and is present in an amount of about 5% by weight.

24. The dosage form of claim 22, wherein said polymer is *Methocel*® and is present in an amount of about 10% by weight.

25. The dosage form of any one of claims 17 to 24, which is in the form of a tablet for oral administration.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/CA 98/00750

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 C08B30/14 A61K9/20

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 C08B A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P,X	WO 98 05688 A (COÖPERATIVE VERKOOP- EN PRODUCTIEVERENIGING VAN AARDAPPELMEEL EN DERIV) 12 February 1998 see page 1, line 1 - line 6 see page 2, line 13 - line 18 see page 4, line 32 - page 6, line 15 see page 8, line 16 - page 11, line 2; claims --- -/--	1,2,4, 14-19,25

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

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"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
1 December 1998	10/12/1998
Name and mailing address of the ISA European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Authorized officer Mazet, J-F

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Form PCT/ISA/210 (second sheet) (July 1992)

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	EP 0 499 648 A (NATIONAL STARCH AND CHEMICAL) 26 August 1992 cited in the application see abstract see page 2, line 41 - line 47 see page 3, line 40 - line 44 see page 3, line 51 - line 52 see page 4, line 2 - line 18 see page 4, line 28 - line 35 see page 4, line 50 - page 5, line 5 see page 5, line 21 - line 28 see page 5, line 49 - line 56 see page 6, line 30 - page 7, line 7	1-9, 12-18, 21,25
X	WO 96 09815 A (COÖPERATIVE VERKOOP- EN PRODUCTIEVERENIGING VAN AARDAPPELMEEL EN DERIV) 4 April 1996 cited in the application see page 2, line 7 - line 15 see page 3, line 16 - line 26 see page 4, line 6 - page 5, line 18 see page 9, line 7 - page 11, line 29 see claims	1,2,4,5, 12-17,25
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Information on patent family members

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PCT/CA 98/00750

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(57) Abstract

A process is disclosed for the manufacture of an excipient useful for the controlled release of an active agent. In this process, a starting material consisting of starch or high amylose starch is subjected to a gelatinization in an aqueous medium. When the starting material consists of starch having an amylose content of less than 50 % by weight, the gelatinized material is subjected to an enzymatic debranching treatment so as to obtain a gelatinized debranched starch having a short amylose chain content of at least 50 % by weight. When the starting material consists of starch having an amylose content of at least 50 % by weight or of a high amylose starch having an amylose content up to 80 % by weight, the gelatinized material is optionally subjected to an enzymatic debranching treatment so as to obtain a gelatinized debranched starch having a short amylose chain content of 20 % to 50 % by weight. The so obtained gelatinized and optionally debranched starch is further subjected to a thermal dehydration in order to obtain the requested excipient in form of a powder. Also disclosed is a dosage administration form for the sustained release of one or more active agents in the form of a powder. This form which is preferably a tablet, comprises the active agent(s) in admixture with the above excipient in such an amount as to achieve the requested sustained release.

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AMENDED CLAIMS

[received by the International Bureau on 8 February 1999 (08.02.99);
original claims 1-25 replaced by new claims 1-24 (4 pages)]

1. A process for the manufacture of an excipient useful for the controlled release of an active agent, comprising the steps of:

a) providing a starting material selected from the group consisting of starch and high amylose starch;

b) subjecting the starting material to a gelatinization in an aqueous medium:

c) when the starting material consists of starch having an amylose content of less than 50% by weight, subjecting said gelatinized material to an enzymatic debranching treatment so as to obtain a gelatinized debranched starch having a short amylose chain content of at least 50% by weight; and

when the starting material consists of starch having an amylose content of at least 50% by weight or of a high amylose starch having an amylose content up to 80% by weight, optionally subjecting said gelatinized material to an enzymatic debranching treatment so as to obtain a gelatinized debranched starch having a short amylose chain content of 20% to 50% by weight, and

d) drying the aqueous gelatinized and optionally debranched starch obtained in step c) in order to obtain the requested excipient in form of a powder,

characterized in that:

in step c), the enzymatic debranching treatment is carried out using a debranching enzyme capable of hydrolyzing the amylopectin molecules, exclusively;

in step d), the drying is carried out by subjecting the aqueous gelatinized and optionally debranched starch to a thermal dehydration; and

in the case where the aqueous gelatinized and optionally debranched starch obtained in step c) has been cooled and kept at a temperature in the range of 1 to 20°C for a given period of time, said aqueous gelatinized and optionally debranched starch is thermally treated at a temperature higher than 100°C prior to being subjected to the thermal dehydration.

2. The process of claim 1, wherein:

in step b), the gelatinization consists of a thermo-mechanical treatment of an aqueous dispersion of the starting material.

3. The process of claim 2, wherein the aqueous dispersion contains from 1 to 20% by weight of the starting material and the thermo-mechanical treatment of this aqueous dispersion is carried out in a scraped-surface heat exchanger at a temperature ranging from 110 to 160°C for 5 to 60 minutes.

4. The process of any one of claims 1 to 3, wherein:

in step c), the enzymatic debranching treatment is carried out with pullulanase at a pH in the range of 3.5 to 6 and a temperature in the range of 35 to 65°C for 1 to 24 hours.

5. The process of any one of claims 1 to 4, wherein:

in step d), the thermal dehydration is achieved by spray-drying of the aqueous gelatinized and optionally debranched material in the form of a solution that contains from 0.5 to 15% by weight of said material and is at a temperature of 20 to 90°C.

6. The process of claim 5, wherein the spray-drying is carried out with a spray-nozzle or rotating disc having an inlet temperature of 175 to 350°C and an outlet temperature of 60 to 135°C.

7. The process of claim 6, wherein the solution contains from 4 to 12% by weight of the aqueous gelatinized and optionally debranched material and is at a temperature of 40 to 70°C.

8. The process of any one of claims 1 to 7, comprising the additional steps of:

e) subjecting the powder obtained in step d) to a granulation.

9. The process of claim 8, wherein, in step e), the granulation is a wet granulation carried out in a fluid bed or high shear granulator.

10. The process of claim 8, wherein, in step e), the granulation is a dry granulation carried out in a roller compaction apparatus.

11. The process of any one of claims 1 to 10, wherein:
in step a), use is made of a high amylose starch containing at least 50% by weight of amylose as said starting material.

12. The process of claim 11, wherein said high amylose starch contains 70% by weight of amylose.

13. The process of any one of claims 1 to 10, wherein:
in step a), use is made of a common or waxy starch as said starting material.

14. The process of claim 13, wherein said common or waxy starch is cross-linked or substituted.

15. An excipient useful for the controlled release of an active agent, said excipient being in the form of a powder and being obtained by the process of any one of claims 1 to 14.

16. A dosage administration form for the sustained release of at least one active agent in the form of a powder, said form comprising said at least one active agent in admixture with an excipient as claimed in claim 15, said excipient being present in such an amount as to achieve the requested sustained release.

17. The dosage form of claim 16, containing at least 20% by weight of said excipient.

18. The dosage form of claim 16, containing at least 60% by weight of said excipient.

19. The dosage form of claim 16, containing at least 94% by weight of said excipient.

20. The dosage form of claim 17 or 18, further containing up to 40% by weight a polymer that becomes viscous in the presence of water and thus may fill cracks formed in the form during its dissolution.

21. The dosage form of claim 20, wherein said polymer is selected from the group consisting of *Carbopol*® and *Methocel*®.

22. The dosage form of claim 21, wherein said polymer is *Carbopol*® and is present in an amount of about 5% by weight.

23. The dosage form of claim 21, wherein said polymer is *Methocel*® and is present in an amount of about 10% by weight.

24. The dosage form of any one of claims 16 to 23, which is in the form of a tablet for oral administration.

STATEMENT UNDER ARTICLE 19

The original set of 25 claims has been deleted and replaced by a new set of 24 claims.

New claim 1 is cast into two parts in order to put emphasis on the characterizing features of the invention. Support for this new claim can be found in original claims 1 and 8 and on page 9, lines 19 to 26 and page 10, lines 20 to 25 of the original description.

New claims 2 and 3 are copies of original claims 2 and 3.

New claim 4 substantially corresponds to original claim 4, except that the reference made therein to use of starch as starting material has been deleted.

New claim 5 substantially corresponds to original claim 5, except that the word --*aqueous*-- has been added before the word *"gelatinized"* and the word *« eventually »* has been replaced by the word --*optionally*-- at line 3 thereof.

New claim 6 is a copy of original claim 6.

New claim 7 substantially corresponds to original claim 7, except that the word --*aqueous*-- has been added before the word *"gelatinized"* and the word *« eventually »* has been replaced by the word --*optionally*-- at line 2 thereof.

New claims 8 to 24 are substantially correspond to former claims 9 to 25, respectively.

It is worth noting that the statement of the invention on page 8 of the description presently on file should be amended to conform to the invention as now reflected in new claim 1.